GENOME-WIDE ASSOCIATION STUDIES

Genome-wide association studies in diverse populations

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Abstract | Genome-wide association (GWA) studies have identified a large number of SNPs associated with disease phenotypes. As most GWA studies have been performed in populations of European descent, this Review examines the issues involved in extending the consideration of GWA studies to diverse worldwide populations. Although challenges exist with issues such as imputation, admixture and replication, investigation of a greater diversity of populations could make substantial contributions to the goal of mapping the genetic determinants of complex diseases for the human population as a whole.

Genome-wide association studies
Study designs in which many markers spread across a genome are genotyped, and tests of statistical association with a phenotype are performed locally along the genome.

Genotype imputation
Probabilistic prediction of genotypes that have not been measured experimentally.

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Over the past few years, genome-wide association studies (GWA studies) have produced numerous successes in identifying genetic variants that contribute to complex human traits[1,2]. Several factors are recognized[3,4] as having markedly increased the number of genotype–phenotype associations documented for a wide range of phenotypes[5,6]. These include increasingly dense sets of genetic markers and larger sample sizes, improved genomic variation resources, and new statistical techniques for genotype imputation[7,8] and meta-analysis[9,10] that leverage these resources.

However, with a few exceptions, GWA studies have been centred on populations of European descent (BOX 1), and the degree to which knowledge gained from these studies is transferable to other populations has not been extensively investigated. Researchers have begun to seek additional groups in which to investigate widely distributed phenotypes, to study new phenotypes that are more prevalent in non-European populations and to establish the generality of findings obtained initially in Europeans and European-Americans. Indeed, recent reports on Chinese[11,12], Japanese[13,14] and Korean[15,16] populations and on Pacific Islanders from Kosrae[17,18] are some of the first in a new wave of GWA studies in non-European populations.

GWA studies in non-European populations may raise several challenges. Will the same results observed in Europeans be detected in diverse worldwide populations? Will causal variants have similar allele frequencies and disease risk in different populations? What factors will be the sources of differing results across groups? As the human genetics community diversifies the populations in which GWA studies are performed, the effort that is likely to be expended on this research program motivates careful consideration of the issues involved in designing the new wave of GWA studies and in interpreting their outcomes.

We argue that expansion of GWA studies to diverse populations is important not only for the ultimate goal of bringing medical advances resulting from genome science to populations worldwide but also for the considerable scientific benefits in characterizing risk variants beyond what can be achieved with populations of European descent alone. We begin by reviewing factors that have contributed to the successes of GWA studies in Europeans. Next, we describe how consideration of diverse populations has the potential to build on these successes. We then discuss the challenges inherent in GWA studies in diverse populations and the role of population-genetic modelling in investigating variation among GWA results across populations. We conclude with a discussion of how further development of genomic resources has the potential to improve prospects for GWA studies in diverse worldwide populations.

Successes in Europeans

Factors influencing the choice of study population. Owing to the expense involved in the execution of GWA studies, it was sensible to perform the first studies in a set of closely related populations for which shared resources could be used. As a first step, a focused effort in which GWA studies of many phenotypes were conducted largely in the same populations — and even in the same samples — had several advantages over a dispersed effort that would have considered a larger collection of

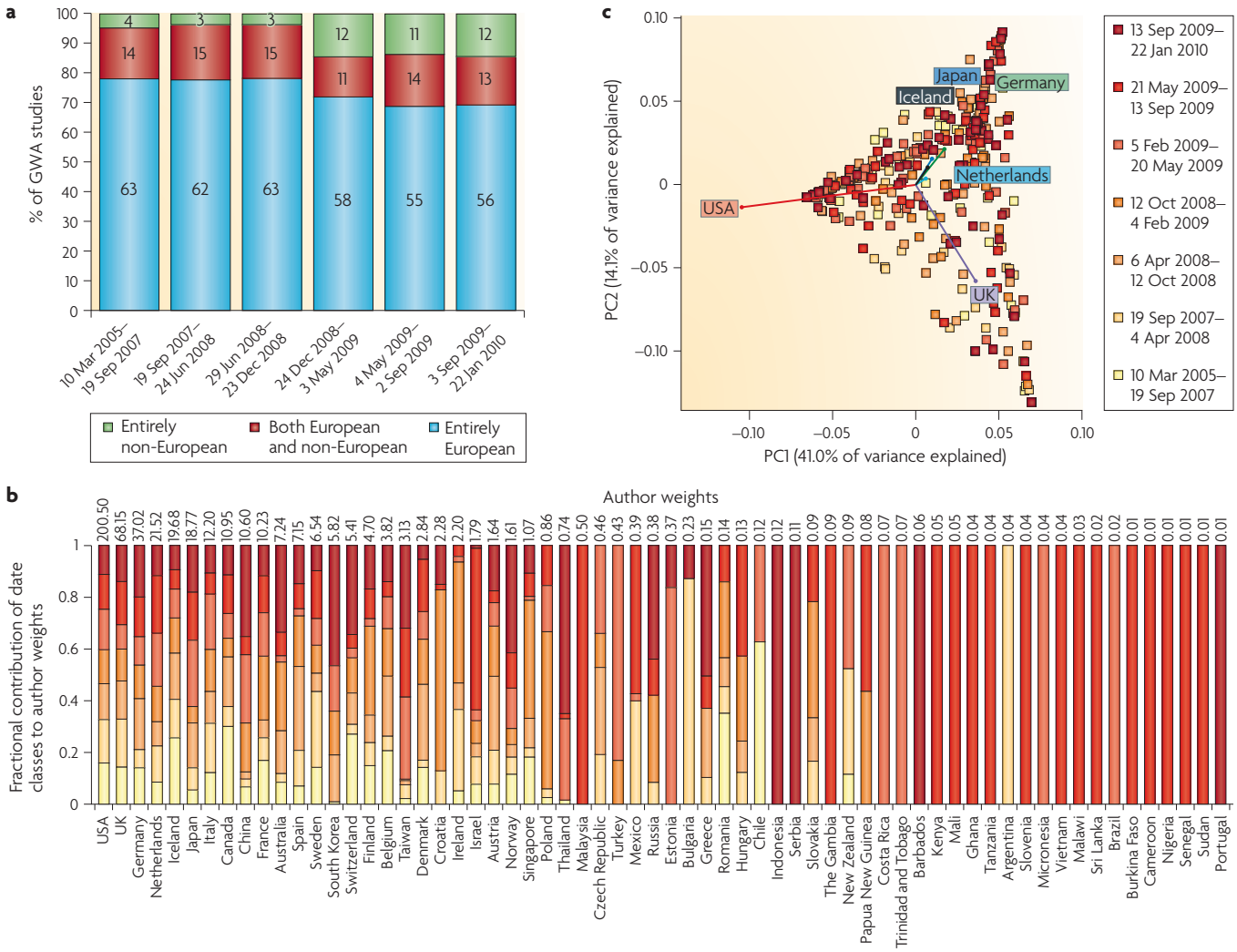
Box 1 | **Populations in past genome-wide association studies**

To assess the extent to which non-European populations have been incorporated into genome-wide association (GWA) studies, we examined the distribution of study populations across 492 GWA articles in the National Human Genome Research Institute (NHGRI) catalogue of GWA results[6,130]. This database provides a manually curated list of SNP–phenotype associations ($P < 10^{-5}$) identified in studies with at least 100,000 SNPs. Article classifications were assessed independently by two raters, with discrepancies resolved by consensus in discussions with a third rater. In the figure, part **a** tabulates classifications based on whether articles used individuals of European descent, individuals of non-European descent or a combination of individuals of European and non-European descent. Eight articles that provided insufficient information about study subjects are omitted, so that each bar represents 80 or 81 articles, grouped by date. The later date ranges are narrower, indicating that in more recent time periods, more studies have been performed per unit time.

The figure illustrates that most studies (~75%) use populations of European descent exclusively. It is likely that this value underestimates the true percentage of GWA effort devoted to populations of European descent, as the tabulation counts as 'both European and non-European' studies in which non-Europeans comprise a small fraction of overall study subjects or in which non-Europeans are part of replication samples examined only for a small number of SNPs. However, a slight trend over time suggests that studies with non-European populations have begun to constitute a larger proportion of the full collection of studies.

We further examined the representation of non-European populations by considering the diversity of the investigators performing the studies (part **b**). For each article analysed, we assigned weight n_k/n to country k, where n_k is the number of authors with affiliations in country k (splitting multiply affiliated authors evenly across affiliations), and n is the total number of authors of the article (excluding consortium authors). To examine temporal trends in country representation, the 473 articles (an additional eleven articles with uncertain author affiliations or consortium-only authors were omitted) were divided into seven chronological groups of near-equal size, and for each country, weights were summed across articles to obtain a total 'author weight' in each date class. Darker colours represent more recent time periods.

Analysis of GWA author weights reveals that the number of countries represented and the representation of non-European countries, such as China, South Korea and Taiwan, has been increasing. Part **c** shows a plot of the first two principal components (PC1 and PC2) of a matrix of country representation vectors (n_1/n, n_2/n, n_3/n, and so on), with one point for each of the 473 articles represented in part **b**. The vectors shown for the six countries with the highest author weights represent the loadings of these countries for PC1 and PC2, describing the contributions of these countries to the first two principal components. The principal components analysis plot identifies three main categories of articles — those with many UK authors, those with many US authors, and those with many authors elsewhere. Many of the most recent articles, represented by the darkest points, lie near the upper corner ('elsewhere') or along the upper edge (collaborations between authors 'elsewhere' and US authors).



populations. The focus on fewer populations aided the development of standard SNP panels, which were assembled based on their variability in those populations. It facilitated the use of shared controls in large studies of multiple phenotypes, reducing the effort required for sample collection and genotyping. Finally, it led to the collection by separate investigators of commensurable samples, enabling large meta-analyses with closely related populations.

Given these advantages of focusing on specific populations, populations of European descent were a natural choice for early GWA studies. Several European populations with a strong history of human-genetic research — such as the populations of Finland, Iceland and Sardinia — are large enough to make it possible to conduct studies with large samples in the setting of a comparatively homogeneous population. In addition, extensive collaborations and long-term genetic studies had already been established involving investigators from European countries and from non-European countries with large populations of European descent, such as Australia, Canada and the United States.

Population-genetic factors. Beyond the practical considerations that contributed to a focus on populations of European ancestry, specific population-genetic properties of the European population have facilitated the successes of GWA studies in groups of European origin. Allele-frequency variation across populations — a source of false-positive findings in association studies[19–21] — is less pronounced in Europe than in other geographic regions[22–27]. Although large population-genetic studies have detected subtle geographic gradients in allele frequencies across the European continent[28–30], as well as within individual countries[31,32], well-designed GWA studies in Europeans have generally controlled for the effects of underlying allele-frequency variation, and generally the identification of false positives due to population structure has not been a problem.

The comparatively low level of population structure has further contributed to GWA successes in Europeans through the utility of the HapMap CEU panel — the 'Centre d'Étude du Polymorphisme Humain (CEPH) European' collection of 30 European-American families genotyped at high density by the International HapMap Project[33,34]. Early GWA studies used a tag-SNP approach[33,35,36], in which each SNP in a genome-wide subset of SNPs was tested for disease association. It was hoped that each true disease SNP not genotyped in a study would be 'captured' through a minimal level of statistical association, or linkage disequilibrium (LD)[37–39], with an informative nearby tag SNP included among the genotyped SNPs. The existence of a true disease SNP in an association study would then be detectable through separate associations of the disease SNP and the phenotype with the tag SNP.

In most cases, tag SNPs chosen with the HapMap CEU panel were indeed 'portable' to studies of common variants in other Europeans[36,40]. Important determinants of tag-SNP portability to a target population are the similarity of the target population to the reference panel from which the tag SNPs were selected, and LD levels in the target population[41]. LD in Europeans is moderate compared with other populations[42,43], so Europeans are not disadvantaged in the tag-SNP approach by this variable. Furthermore, portability is enhanced in Europeans owing to the low level of population structure and the resulting high level of genetic similarity between most European populations and the CEU sample[41].

The combination of the various population-genetic factors with the pragmatic factors affecting the choice of study populations has uniquely favoured European populations in GWA studies. These factors provide part of the explanation for two outcomes: European GWA studies have produced many successes that can be replicated in different sets of individuals from the same European population as that in which the association was originally detected; and associations in one population of European descent are often replicable in other European populations, sometimes in groups that are quite geographically distant within the European continent.

The case for more populations

The advantages of European populations in GWA studies suggest that Europeans might productively be used for finding risk variants in non-Europeans. However, European populations contain only a subset of human genetic variation. Populations vary in terms of allele frequencies, biological adaptations and other properties that affect the detectability and importance of risk variants. Several observations suggest that no single population is sufficient for fully uncovering the variants underlying disease in all populations.

First, risk variants can differ in their occurrence across populations. A high-risk variant might only occur in certain populations, as has recently been seen for a cardiomyopathy risk variant at myosin binding protein C, cardiac (*MYBPC3*) that has a frequency of ~4% in populations of the Indian subcontinent but is rare or absent elsewhere[44]. Such variants differ substantially in their relevance to different groups.

Second, even if the same variant is present in diverse populations, allele frequencies might differ[45,46], as has been seen at transcription factor 7-like 2 (*TCF7L2*) and potassium voltage-gated channel, KQT-like subfamily, member 1 (*KCNQ1*) in type 2 diabetes (BOX 2). The particular histories of recombination, mutation and divergence of genealogical lineages in the various populations can influence the ease with which a variant can be mapped, so a variant might be more easily detectable in some populations than in others[47,48] (FIG. 1). Populations with lower LD (in which correlations between genotypes extend over shorter distances along a chromosome) might be more suitable for finely localizing a risk variant once its genomic region has been identified; this is because the genomic distance between disease-associated markers and true risk variants is likely to be smaller in such populations[49]. Localization methods can potentially capitalize on LD differences across populations by identifying variants for which a causal relationship with disease underlies divergent patterns of association signals in a genomic region[50].

Principal component
A composite variable that summarizes the variation across a larger number of variables, each represented by a column of a matrix.

Loading
In a principal components analysis, a quantity that represents the contribution of one of the original variables (columns of the data matrix) to one of the principal components.

SNP
A nucleotide site at which two or more variants exist in a population. Most SNPs in genome-wide association studies are biallelic.

Tag SNP
A SNP chosen from a larger set of available SNPs for use in an association study. Tag SNPs are generally selected on the basis of favourable linkage disequilibrium properties.

Linkage disequilibrium
A statistical association in the occurrence of alleles at separate loci.

Tag-SNP portability
The utility of SNPs chosen as tags in one population for use as tags in another population.

Box 2 | **Common variants for type 2 diabetes**

Over the past 3 years, large-scale genetic association studies have uncovered an impressive array of common variants that confer risk for type 2 diabetes (T2D) in populations of European origin[131] and now also in East Asian populations[13,14]. Genome-wide association (GWA) studies of T2D provide a microcosm of the variety of issues that arise when considering association results across populations.

In a study in Icelanders, Grant *et al.*[132] identified common alleles in transcription factor 7-like 2 (*TCF7L2*) as being associated with T2D, a finding that has been confirmed in many populations, including other Europeans[133,134], West Africans[135], East Asians[136], South Asians[137] and Mexican-Americans[138]. These *TCF7L2* SNP alleles seem to have the strongest effect on T2D risk among common variants in Europeans. By analysing data in Europeans and West Africans, Helgason *et al.*[135] narrowed the likely *TCF7L2* candidate region using differences in association strength with several *TCF7L2*-region SNPs in these populations. Subsequent analysis of T2D association in East Asians suggests that whereas genetic effect sizes for these *TCF7L2* variants are similar in East Asians, risk allele frequencies are substantially lower, so much larger samples are needed to identify the association[139].

The first T2D GWA studies in East Asians identified T2D risk variants in potassium voltage-gated channel, KQT-like subfamily, member 1 (*KCNQ1*)[13,14]. A recent meta-analysis in Europeans carried out by the DIAGRAM Consortium detected this same signal with a similar effect size, but at a level not even approaching genome-wide significance due to a much lower risk allele frequency (DIAGRAM Consortium, personal communication). Interestingly, this same meta-analysis identified a second genome-wide significant T2D association signal ~150 kb from those discovered in East Asians.

These examples show the value of carrying out large-scale genetic association studies in multiple populations to elucidate similarities and differences in genetic architecture and to help narrow candidate regions for identified disease-predisposing variants.

Third, diseases can have differences in prevalence across populations. Although a large portion of this variation undoubtedly results from non-genetic factors, disease prevalence affects both the practicality of obtaining the large sample sizes required by GWA studies for detecting variants with small effects and the relevance to a population of the findings. A limited population focus risks underemphasizing diseases for which prevalence is high in non-European populations, or reducing the power of a study compared with one that uses a larger sample from higher-prevalence populations.

Fourth, risk variants can have different effect sizes in different populations, so that variation across populations can exist in the underlying determinants of the same disease[51]. The existence of these risk differences, such as for the apolipoprotein E (*APOE*) ε*4* allele in Alzheimer's disease[52], implies that the risk variants that are most relevant in a population might be most easily detected by using samples from the population itself, rather than by using samples from other populations.

The case for using diverse populations in GWA studies has recently been strengthened by the observation that the proportion of phenotypic variation explained by variants discovered through GWA is typically small[53]. GWA studies have focused on common variants — alleles that were typically present in ancestral African populations and that spread worldwide with ancient human migrations. Rare variants, which have not been examined to the same extent, provide one possible genetic source for unexplained phenotypic variation[54–56]. They might even be responsible for some association signals that are currently attributed to common variants[47,57]. Because rare variants are usually more recent in origin (as they have not had enough time to increase in frequency and become common), they are more likely to be geographically localized. Separate populations are therefore more likely to differ in their collection of rare alleles than in their collection of common alleles (FIG. 2).

These various reasons — differences in disease-allele frequency and LD patterns, phenotypic prevalence differences, differences in effect size and differences in rare variants — provide the scientific motivation for GWA studies in diverse populations. Some variants that act in all populations might be more easily identifiable in certain groups owing to the properties of LD and allele frequency in those groups. For some phenotypes with low prevalence in Europeans, studies might be more practical in other groups[49]. In addition, the use of multiple populations is the only way to uncover true biological variation in underlying risk variants, including biological variation resulting from differences across populations in the occurrence of rare risk alleles.

Challenges in non-Europeans

The properties of marker ascertainment, tag-SNP portability and population structure that have been favourable to association mapping in Europeans instead pose challenges for studies in many non-European populations.

Marker ascertainment. Several investigations have found that the SNPs typically used in GWA studies are in various ways non-random[58,59]. They can have comparatively higher minor allele frequency (MAF) in Europeans and therefore higher expected heterozygosity than might be predicted on the basis of what is known about other types of markers that have less ascertainment bias (FIG. 3). These observations, which are likely to result from a focus on populations of European ancestry in the initial detection of SNPs, in turn affect the relative proportion of the genome suited to mapping in different populations. Because of ascertainment effects in the development of marker panels, the fraction of the genome that lies within a specified physical distance of at least one variable marker in a standard panel varies across populations. Additionally, the LD statistic r^2 (which measures whether a locus is 'covered' by a panel, typically on the basis of its maximal LD with some marker from the panel[60]) depends on marker-allele frequencies[61,62]; intermediate-MAF markers have greater potential to produce high r^2 values than markers at a range of other minor allele frequencies[63]. Therefore, ascertainment bias that produces many low-MAF markers in a population can lead to decreased potential to detect phenotypically important alleles across the full range of possible allele frequencies, ultimately reducing the genome-wide utility in the population of standard marker panels.

Minor allele frequency
The frequency of the less frequent allele at a biallelic genetic locus.

Expected heterozygosity
The probability for a locus that two alleles drawn from its allele-frequency distribution are distinct.

Ascertainment bias
A distortion in results due to the use of a subsample that, in a systematic manner, fails to properly represent a larger sample.

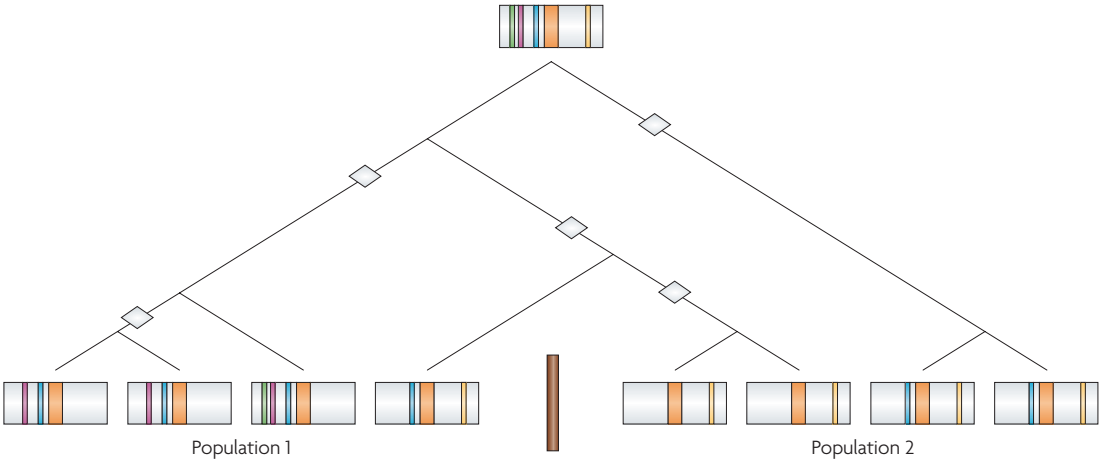


Figure 1 | **Differences in 'mappability' of a risk variant between two populations with different linkage disequilibrium patterns.** A disease mutation (orange rectangle) occurs on an ancestral chromosome that contains several marker alleles (green, pink, blue and yellow). Over time, recombination events (diamonds) break down the correlations between the disease mutation and the marker alleles. However, the recombination history differs for populations 1 and 2, separated by a barrier to gene flow (brown vertical line). Consequently, if the pink or blue allele were examined in population 1, a disease association might be found, but it might not be found in population 2. A similar situation applies for the yellow allele, with the roles of the populations reversed. Figure is modified, with permission, from REF. 121 © (2009) John Wiley and Sons.

Tag-SNP portability. Ascertainment issues might have contributed to the decreased level of tag-SNP portability seen in some non-European populations compared with predictions based on the LD levels of these populations[41]. Although tag SNPs chosen from the HapMap are generally portable to most non-European populations[36,40], portability is reduced in low-LD populations and intermediate-LD indigenous populations that are genetically distant from HapMap reference panels[41]. Tag-SNP portability can potentially be improved in populations that are genetically intermediate between the primary HapMap populations by using a mixture strategy to select SNPs for genotyping panels. In this approach, tag SNPs are selected to be informative for a mixture of haplotypes drawn from multiple HapMap groups rather than from a single group[64,65]. However, this mixture strategy does not solve the problem of low portability in sub-Saharan African populations, in which LD levels are considerably lower than in other populations[43,49,66].

Genotype imputation. Recently, tag-SNP analyses have been augmented by a genotype-imputation approach, in which data analysis is not restricted to SNPs that have been experimentally genotyped. In imputation-based GWA studies[7,8,67], densely genotyped reference individuals, typically from the HapMap Project, provide information for predicting the genotypes at SNP positions measured in the reference data but not in the study sample. These predicted genotypes are then tested for disease association. Imputation is possible because two haplotypes that are identical for a set of nearby markers are likely to share the intervening chromosomal stretch identically by descent. Therefore, if one of the two haplotypes is genotyped more densely than the other, genotypes at unmeasured positions in the more sparsely genotyped haplotype can be predicted by copying the genotypes from the more densely genotyped haplotype. Genome-wide imputation of study haplotypes proceeds by locally copying the most appropriate reference haplotypes in a probabilistic manner.

In imputation studies, the reduced portability of tag SNPs to African populations and to populations that, compared with reference groups, are genetically intermediate has resulted in reduced imputation accuracy for these populations[68] and, consequently, reduced statistical power for imputation-based association mapping[69]. The accuracy of imputation depends largely on the same two factors that influence tag-SNP portability. First, the overall level of LD in a study population reflects the distance over which the genotypic correlations that permit imputation extend, so imputation is more accurate in high-LD populations[68]. Second, imputation accuracy is influenced by the level of genetic relationship of the study population to the reference population[8,68], which affects the utility of the haplotypes copied from the reference population when imputing genotypes in the study population. In an assessment of imputation accuracy in 29 populations worldwide, imputation accuracy based on HapMap reference panels was highest in European populations closely related to the HapMap CEU panel and lowest in African populations and populations that were genetically intermediate between the panels[68] (FIG. 4). As described above for the portability of tag SNPs, the use of mixture panels as reference data in imputation algorithms can improve imputation accuracy for GWA studies in genetically intermediate populations, but imputation in low-LD African populations continues to be a particular challenge[49].

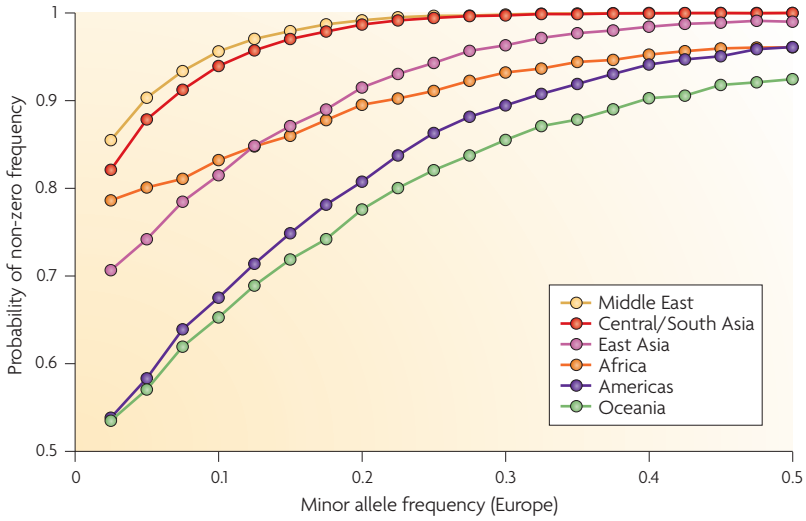


Figure 2 | **Effect of frequency in Europe on the occurrence of an allele in other regions.** The figure illustrates that alleles that are more common in one group, in this case Europeans, are more likely to be present in other groups. It also shows that populations that are geographically closer to Europe, such as populations of the Middle East, tend to have more alleles shared with Europeans than more geographically distant populations, such as those of Oceania. The figure is based on SNP data from supplementary figure twenty-one of REF. 43, which used 512,762 autosomal SNPs in indigenous populations from the Human Genome Diversity Cell Line Panel[140], and which standardized sample sizes across groups by evaluating allele frequencies in samples of size 40.

Admixed populations

In the effort to improve the potential of GWA studies for diverse human populations, African populations are not the only populations that pose substantial challenges. As described in the previous section, tag-SNP and imputation studies have found that indigenous populations that are genetically intermediate between reference groups are among those that require special consideration. In these cases, the challenges result largely from the way in which genomic resources have been developed rather than from intrinsic population properties. However, a second form of intermediate population exists in which the challenges are in fact intrinsic.

In admixed populations, individual genomes can be viewed as mosaics of ancestry segments, with different segments arising from different 'parental' populations that participated in an admixture process. Admixed populations often have high variation across individuals in the proportions of ancestry from the various source groups[70–72], and in the same way that the use of multiple subgroups of a larger population in an association study can give rise to false-positive associations, variation in admixture proportions can produce spurious associations of genotypes and phenotypes through their separate associations with ancestry[73].

Heterogeneity of admixture has posed a barrier to association mapping in admixed populations. These populations have instead been considered with other designs, such as admixture mapping, in which genomic segments with excess ancestry from a high-prevalence parental population are identified as potential locations for risk variants[74–77]. The utility of admixture mapping, which has had some success in mapping loci for traits with strong differences in phenotypic distribution among parental populations[78–81], has relied on its relative efficiency compared with GWA. Whereas GWA has typically used tens to hundreds of thousands of markers (or more), admixture mapping requires only a few thousand markers for estimating the ancestry of genomic segments[82–85]. However, GWA designs have improved, and the efficiency of GWA now exceeds that of admixture mapping over a broad range of possible values for model parameters[86]. Future analyses in admixed populations might rely on a combination of GWA and admixture-mapping principles that considers unusual local ancestry estimates jointly with association signals. In addition, because admixture mapping requires fewer markers, it might continue to be valuable in genomic regions that are poorly covered by typical GWA marker sets.

In the imputation context, it has been largely unclear whether genotypes in an admixed population can be most accurately imputed using a mixture of reference panels from the parental populations or using a comparable reference panel from the admixed population itself. Numerous techniques are now available for inferring ancestry blocks along the genome under study[87–91], and one recent approach uses imputation accuracy as a basis for evaluating inference of ancestry blocks[92]. These developments now offer the possibility of improving imputation in admixed populations by integrating the inference of admixture and missing genotypes[93], either by locally imputing from parental reference panels along the genome (FIG. 5) or by concurrently imputing genotypes and inferring ancestry. Although evaluations in admixed populations of the performance of different imputation approaches have not yet used local ancestry[94], it is likely that the intrinsic challenges of working with admixed populations in GWA studies can be surmounted or at least reduced.

Population-genetic modelling

We have seen that information on the population-genetic properties of individual populations and sets of populations is useful for understanding the features and limitations of GWA studies in diverse populations. Population-genetic data and modelling have had important roles in the planning of GWA studies from the early stages[3,95], and modelling efforts can now help to address concerns about the similarities and differences among GWA results in separate populations.

Population-genetic models begin from the perspective that the factors that affect the genealogical descent of a disease mutation — such as migrations, changes in population size, natural selection and the local recombination landscape — ultimately affect the distribution of the mutation across individuals in the present. Because the full genetic history of the human population is unknown, population-genetic models based on relatively few parameters can be used instead to simulate plausible histories, to examine the properties of risk variants simulated under the models and to evaluate strategies for detecting these variants.

Admixed population
A population formed recently from the mixing of two or more groups whose ancestors had long been separated.

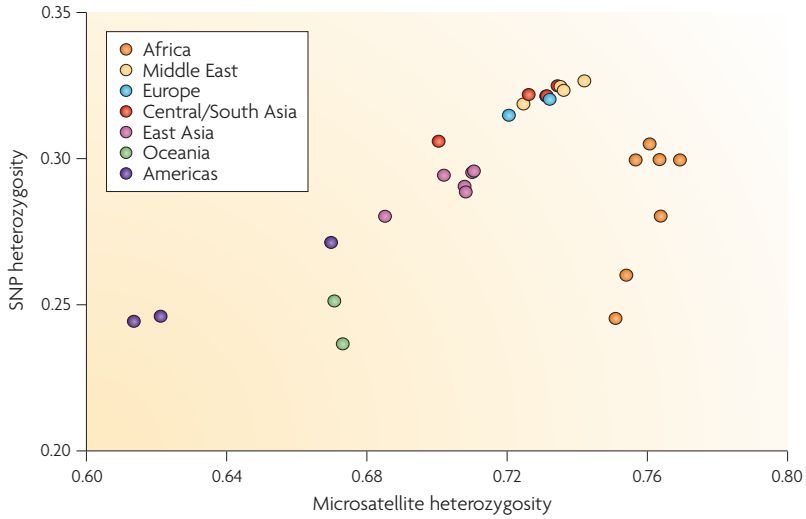


Figure 3 | **Excess SNP variability in Europeans resulting from ascertainment bias.** The *y* axis depicts mean heterozygosity across loci in 443 individuals from 29 populations on the basis of 512,762 autosomal SNPs from an Illumina genotyping panel[43]. The *x* axis depicts mean heterozygosity in the same individuals on the basis of 783 autosomal microsatellite markers[141,142]. Because individual microsatellites, unlike SNPs, are highly variable, microsatellite ascertainment is less dependent on the initial ascertainment sample than is SNP ascertainment[143]. Therefore, the imperfect correlation of SNP heterozygosity with microsatellite heterozygosity might reflect ascertainment bias in the SNP set. The idea for this figure is based on a similar figure in REF. 41.

Many of these models use the coalescent framework[96,97], which provides a flexible, computationally efficient and theoretically grounded approach that can simulate one or more populations retrospectively, back in time from the present.

New population-genetic simulation tools that account for shared descent among individuals, through both the coalescent and through forward-time approaches[98–101], now provide an improved basis for GWA modelling. Simulation programs have incorporated newly appreciated phenomena, such as recombination hot spots[102], as well as approximations and computational advances that improve the potential for simulating large genomic regions[103–106]. Human population-genetic data have been recently used to calibrate evolutionary models[107–112], and further advances in human population genetics offer the potential to make these models increasingly detailed and therefore increasingly relevant for GWA applications.

Independence approximations. A primary use of a population-genetic perspective in the GWA context has been in predicting expected patterns of disease variation[113–115]. However, GWA statistical analysis tools have not yet fully taken advantage of this perspective. From a population-genetic standpoint, all individuals have some degree of relationship through their shared descent in the complete human pedigree. However, in standard GWA analyses, in which alleles that are more common in cases than in controls are identified by testing contingency tables locally along the genome, an implicit assumption is that the genotypes of separate individuals can be treated as independent random variates. Approximating separate individuals as independent has been productive as a first approximation, but more information is potentially available by accounting for correlation among individuals resulting from shared descent. Fine-mapping association methods designed for localization of risk variants seek to consider this shared descent[116–120]; these methods have been informative on a small scale, but a current challenge is to extend them to large data sets.

Similar independence approximations are made in GWA replication analyses, which check for close relationships among sampled individuals but otherwise treat separate studies of non-overlapping samples as independent. A genealogical perspective suggests that replication studies are in fact 'pseudoreplication' studies, as potential correlations could arise from shared genealogy. From this viewpoint, particularly in small populations, separate association studies that identify the same risk variant in a population might not provide the same degree of confirmation as replication studies that are conducted in a context in which events are truly independent[121]. As in the analysis of individual GWA studies, the independence assumption has provided a sensible initial strategy for replication studies, but unlike the case of genealogical dependence within studies, approaches that account for dependence among studies have not yet been considered. The magnitude in real populations of the pseudoreplication effect — the degree to which separate association studies provide the same outcome as a result of shared ancestry of study participants — is unknown, so it remains uncertain how likely a replication study is to detect a risk variant under the hypothesis that the variant has the same disease effect in all populations. The probability of pseudoreplicating a false positive across populations is also unknown. Although efforts have been devoted to statistical issues of replication in relation to sample size and measured effect-size[122,123], studies of the population genetics of replication are in their infancy. As the frequency of replication studies continues to increase, methods for evaluating intrinsic correlations between study outcomes and their effects on interpretations of replication studies would provide a useful development.

Prospects

GWA studies have dramatically increased the number of variants known for numerous complex diseases. They have been remarkably successful for identifying targets of exploration, often suggesting unforeseen directions for research on disease mechanisms, and they have been especially informative for scientists working on diseases for which few if any genetic variants were previously known. At the same time, they have shown that complex genetic diseases are incontestably complex, caused by many variants that have mostly small effects and that are unsuited to immediate risk prediction and clinical use. These results have understandably triggered a series of reflections on the magnitude of the contributions of GWA studies

Microsatellite
A type of genetic marker in which individuals vary in their number of tandemly repeated copies of a short DNA unit.

Coalescent
A specific stochastic process that describes the relationship among genetic lineages sampled in a population.

Recombination hot spot
A region of the genome in which the per-generation recombination rate is substantially elevated above the genome-wide average.

Contingency table
A table of observations of two or more variables that might have a statistical relationship of interest. For each variable, a contingency table places each observation into one of a series of categories.

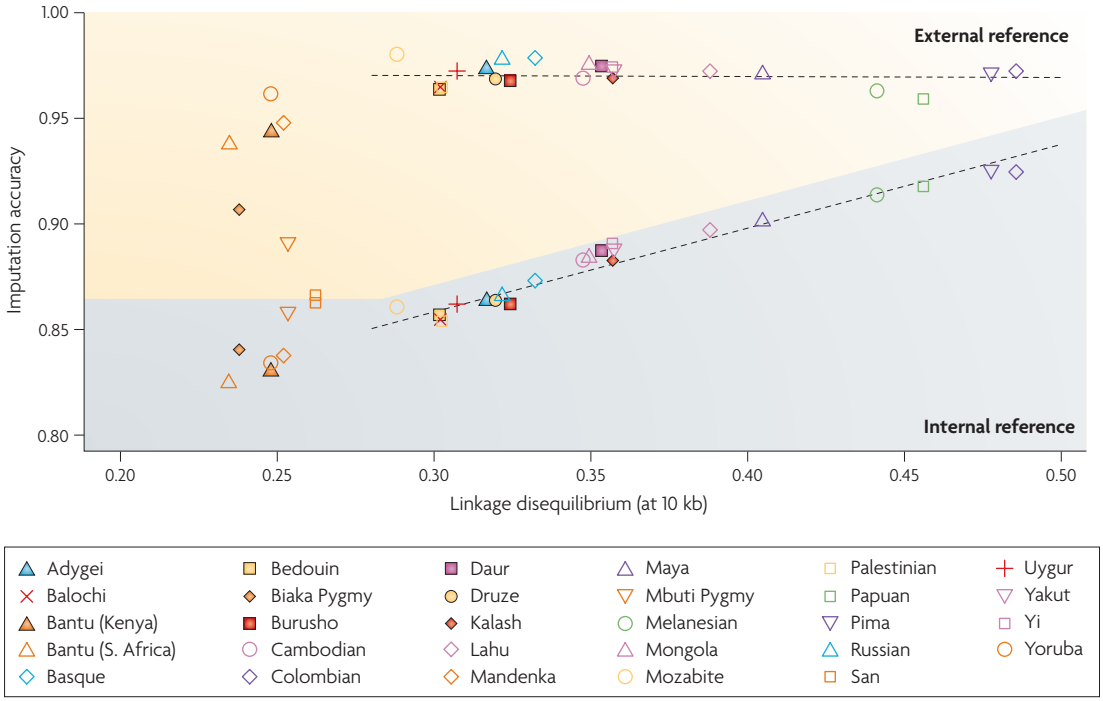


Figure 4 | **Genotype imputation accuracy in 29 populations, with and without external reference panels.** Imputation accuracy is plotted as a function of linkage disequilibrium (LD) measured by mean r^2 at a distance of 10 kb in a genome-wide data set[43]. Genotypes in a genome-wide study are hidden and then imputed with two different designs. In the grey shaded region, genotypes in each population are imputed without an external reference panel, so the information for imputing 'missing' genotypes comes from other individuals in the population. In the yellow shaded region, genotypes in the population are imputed using a large external reference panel, chosen optimally among 36 mixtures of the HapMap CEU (European-American), CHB+JPT (Chinese and Japanese) and YRI (Yoruba) panels. Colour coding for populations follows that of FIG. 3 (Africa, orange; Middle East, yellow; Europe, blue; Central/South Asia, red; East Asia, pink; Oceania, green; Americas, purple). The regression lines exclude the African populations, and they have coefficients of determination 0.003 (external reference) and 0.953 (internal reference). The figure shows that imputation accuracy based on an internal reference is highly correlated with LD. However, imputation accuracy based on an external reference is not correlated with LD (and instead depends largely on the composition of the particular reference panels available). The figure is based on data in scenarios one, three and six in table three of REF. 68.

in general[4,124–127]. GWA is a relatively new approach, and its full contribution will only become clear as the biological properties of the variants it uncovers are further investigated. As the GWA field diversifies its emphasis, attention will shift not only to diverse populations but also to structural variation, interaction effects, rare sequence variation and molecular assays of identified variants.

We and others[128,129] have argued that the use of diverse populations will be an essential component of the next phase of GWA work, and we have discussed the benefits that arise from the consideration of GWA studies in diverse populations. As knowledge gained from GWA becomes relevant to medicine, a concern is that health disparities will emerge owing to the bias towards European populations in GWA studies, but using diverse populations in GWA studies can reduce differences in the understanding of underlying genetic variation across populations. Many GWA studies in diverse populations are now ongoing or are imminent. To achieve their maximal potential, these studies will profit from deeper investigation of such issues as imputation, admixture and replication, as we have described.

The current GWA strategy of using preselected markers to search for risk variants that are common in human populations is giving way to a paradigm of using whole-genome sequence approaches that can search for rare disease-risk variants as well. Future GWA studies — and some studies now in progress — will incorporate partial or complete genome sequences for some or all of the study participants. For many of the same reasons that GWA studies to date have emphasized populations of European descent, early sequence studies might also have a European focus. As we have seen, however, rare risk variants are likely to be more geographically restricted than the common variants that are currently of interest. Consequently, it will be even more important for multiple populations to be considered in sequence-based GWA studies that are aimed at detecting rare variants than in current studies of common variants.

The 1000 Genomes Project, a large-scale community effort aimed at producing genome sequence data on ~2,000 diverse individuals, will facilitate sequence-based GWA studies in diverse populations, serving as a public resource for sequence-based GWA studies in the same way that the HapMap Project provided data for tag-SNP GWA studies. With sequencing, concerns about population biases in marker ascertainment are likely to subside. Furthermore, the larger number of individuals in the 1000 Genomes Project compared with the initial 270 individuals in the HapMap Project permits the examination of a wider diversity of samples. Therefore, the forthcoming genomic resources already under development are expected to improve the conditions for the examination of diverse populations in GWA studies.

At the same time, it must be remembered that the worldwide human population and its distribution of disease-risk variation represent the singular outcome of an evolutionary experiment, and large portions of this experiment continue to remain untapped for their potential to contribute to the modern enterprise of human genetics. Each new genetic resource expands the consideration of human diversity but necessarily provides an incomplete picture of its full extent. Therefore, many opportunities exist for identifying new aspects of genetic variation to examine for future resources, as well as for the creative application of worldwide populations in the discovery of risk variants, in the characterization of known variants and in the facilitation of these efforts through population-genetic modelling and statistical designs. As technological barriers to the production of genomic data continue to fall, it can be hoped that the community will accept the challenge of capitalizing on the full range of human diversity for the next wave of investigations of the variants that underlie human genetic disease.

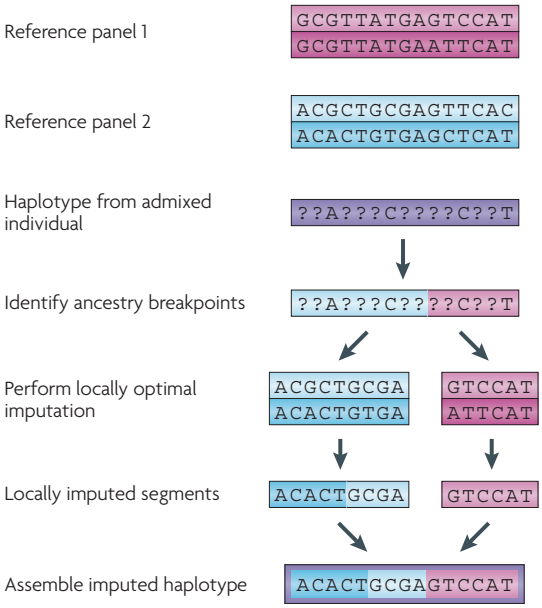


Figure 5 | **Imputation in admixed populations.** Admixture segments are estimated in each individual sampled from a genome-wide association study. Consider reference haplotypes from two separate panels (pink and blue boxes). Separately for each admixture segment of a haplotype, alleles are imputed using reference haplotypes from the same population as the inferred source. Within a source population, a haplotype might have alleles imputed from multiple reference haplotypes; this is depicted on the left, where both haplotypes from the same (blue) source population serve as imputation templates. If admixture estimates for a segment are uncertain, conditional imputations can be used; given each of the possible source populations for the segment, the conditional imputation can be weighted by the probability of the source.

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Competing interests statement
The authors declare no competing financial interests.

DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/gene
APOE | *KCNQ1* | *MYBPC3* | *TCF7L2*
OMIM: http://www.ncbi.nlm.nih.gov/omim
UniProtKB: http://www.uniprot.org

FURTHER INFORMATION
1000 Genomes Project: http://www.1000genomes.org
Human Genome Diversity Cell Line Panel: http://www.cephb.fr/en/hgdp/diversity.php
International HapMap Project: http://hapmap.ncbi.nlm.nih.gov
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